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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,115	04/29/2005	Yoshiko Takayama	2005_0740A	2341

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EXAMINER
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WANG, CHANG YU

ART UNIT	PAPER NUMBER
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1649

NOTIFICATION DATE	DELIVERY MODE
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08/05/2010

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com  
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<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<p><b>Application No.</b> 10/533,115</p>	<p><b>Applicant(s)</b> TAKAYAMA ET AL.</p>	
	<p><b>Examiner</b> CHANG-YU WANG</p>	<p><b>Art Unit</b> 1649</p>	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 20 July 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 20 July 2010. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: \_\_\_\_\_.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 7/20/10  
13. ☐ Other: \_\_\_\_\_.

/Chang-Yu Wang/  
Examiner, Art Unit 1649

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments have been fully considered but they are insufficient to overcome the rejection under 103(a). The rejection is maintained for the reasons made of record in the office action mailed January 20, 2010.

Claim 14 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Nordisk (WO98/58646, published on Dec 30, 1998 as in IDS) in view of Perez-Santonja et al. (Am J. Ophthalmol. 1999. 127:497-504, cited previously), WO98/44922 (Yang et al, published Oct 15, 1998, as in IDS) and WO97/43278 (Ankersen et al, published Nov 20, 1997, as in IDS) as evidenced by Suzuki et al. (see p. 550, abstract, Suzuki et al. Curr Eye Res. 2000. 21:550-553, cited previously) and Fini et al. (see p. S12 2nd col., Fini et al. Arch Dermatol. Res. 1998. 290: S12-S23, cited previously) and the data of cornea (p.3-4, retrieved from the NEI website, [www.nei.nih.gov/health/cornealdisease](http://www.nei.nih.gov/health/cornealdisease), cited previously). The rejection is maintained for the reasons made of record and the reasons set forth below.

On p. 2-3 of the response, Applicant argues that Nordisk describes SSTR2 and SSTR4 are expressed in the iris-ciliary body and retina and refers to treating glaucoma, stroma keratitis, iritis, retinitis, cataract and conjunctivitis. But Suzuki and Fini do not describes that the disease which Nordisk discloses result in decreased corneal sensitivity. Applicant further argues that the other cited references fail to remedy the deficiency. Applicant argues that Nordisk either alone or in combination fails to teach the claimed method. Applicant argues that a skilled artisan would not expect the potency of the claimed invention from the cited references because examples 4-5 in instant specification showed that compound 1 (SSTR2 agonist) and compound 2 (SSTR4 agonist) exert a promoting effect on axon extension at a 10 or 100 times lower concentration. Applicant's arguments have been fully considered but they are not persuasive.

In response, first, as previously made of record, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In addition, the evidentiary references Suzuki and Fini are cited to support the fact that conjunctival inflammation (conjunctivitis) and corneal ulceration caused by stromal keratitis (herpes virus infection on cornea) and stromal ulceration have defective healing of corneal epithelium.

Further, in this case, although Nordisk does not teach that the decreased corneal sensitivity occurs after surgery as recited in instant claim 14, Perez-Santoja teaches that laser in situ keratomileusis to correct myopia or photorefractive keratectomy can decrease corneal sensitivity (see p. 497, abstract & col.2, in particular). Note that laser in situ keratomileusis and photorefractive keratectomy are a surgery that causes decreased corneal sensitivity. Thus, it would have been obvious to a skilled artisan at the time the instant invention was made to use somatostatin, a SSTR2 or SSTR4 somatostatin agonist to recover decreased corneal sensitivity in a subject with a damaged or cut corneal nerve axon wherein the decreased corneal sensitivity results from surgery. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because an eye surgery can cause decreased corneal sensitivity; and somatostatin, a SSTR2 or SSTR4 somatostatin agonist has successfully been used to recover decreased corneal sensitivity in patients with a damaged corneal nerve axon, such as patients with glaucoma, conjunctivitis, inflammation of corneal stroma, stromal keratitis, which are disorders with a damaged corneal nerve and defective corneal epithelium as taught by Nordisk. Thus, the results of recovering decreased corneal sensitivity after surgery using somatostatin, a SSTR2 or SSTR4 somatostatin agonist would have been expected.

Moreover, although Nordisk and Perez-Santoja do not specifically teach that t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-1- carbonyl)amino)propionylamino)hexanoate or 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea as an SSTR2 and SSTR4 agonist respectively, WO98/44922 teach t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-1- carbonyl)amino)propionylamino)hexanoate as an SSTR2 agonist (see abstract; p.2, p.8, p. 13-15, in particular), and WO97/43278 teaches 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea as an SSTR4 agonist (see abstract; p.2-22, in particular). Thus, it would have been obvious to a skilled artisan at the time the instant invention was made to use t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-1- carbonyl)amino)propionylamino)hexanoate or 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea to recover decreased corneal sensitivity in a subject with a damaged or cut corneal nerve axon wherein the decreased corneal sensitivity results from surgery. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because an eye surgery can cause decreased corneal sensitivity, and somatostatin, a SSTR2 or SSTR4 somatostatin agonist has successfully been used to recover decreased corneal sensitivity in patients with a damaged corneal nerve axon, such as patients with glaucoma, conjunctivitis, inflammation of corneal stroma, stromal keratitis, which are disorders with a damaged corneal nerve and defective corneal epithelium as taught by Nordisk. Thus, the results of recovering decreased corneal sensitivity after surgery using t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-1- carbonyl)amino)propionylamino)hexanoate or 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea would have been expected because t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-1- carbonyl)amino)propionylamino)hexanoate is an SSTR2 agonist and 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea is an SSTR4 agonist as taught by WO98/44922 and WO97/43278 respectively.

Accordingly, the rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Nordisk in view of Perez-Santonja et al., WO98/44922 and WO97/43278 as evidenced by Suzuki et al. and Fini et al. and the data of cornea (retrieved from the NEI website) is maintained.

/CYW/  
7/21/10